Improving targeted treatment in early rheumatoid and undifferentiated arthritis

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Chapter 7

AGE AFFECTS JOINT SPACE NARROWING IN EARLY ACTIVE RHEUMATOID ARTHRITIS PATIENTS

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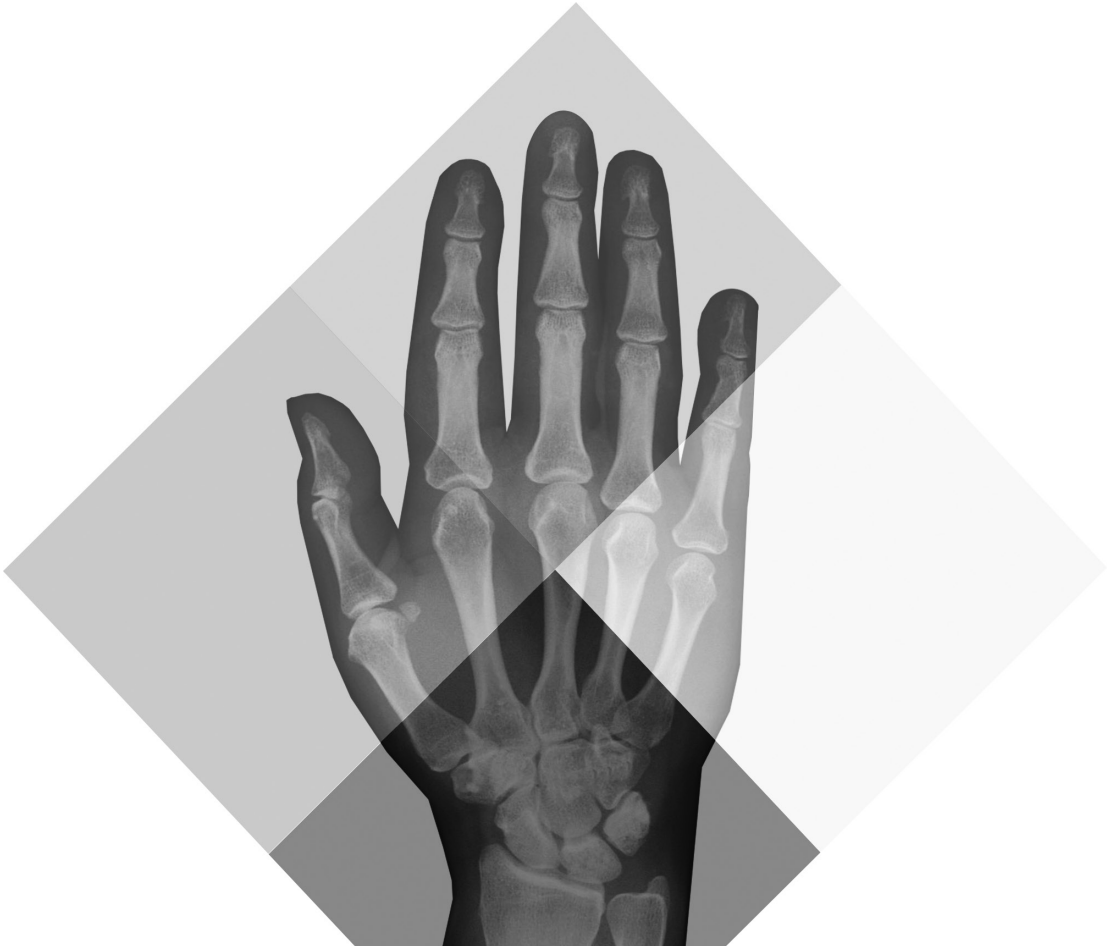

ABSTRACT

Background/purpose

Joint space narrowing (JSN) in rheumatoid arthritis (RA) may be a manifestation of (primary) osteoarthritis becoming more prominent with age. We investigated the severity and predictors of JSN progression among different age-groups.

Methods

Ten year follow-up data of the BeSt study, a randomized controlled treat-to-target trial in early RA were used. Annual X-rays of hands and feet were scored using the Sharp/van der Heijde score (SHS). Subgroups were defined by age at baseline: ≥55, ≥40<55 and <40 years. JSN progression predictors were assessed by Poisson regression.

Results

Baseline JSN scores (median (IQR)) were higher in patients ≥55 (2.0(0.0-6.0)) compared to the other age-groups: 1.0 (0.0-3.0) ≥40<55 and 0.3 (0.0-3.0) <40, p<0.001. After ten years, total JSN and SHS scores were similar in all age-groups.

In patients ≥55 the mean erythrocyte sedimentation rate (ESR) over time (RR 1.02 (95% CI 1.00-1.03)) and the combined presence of rheumatoid factor and anti-citrullinated protein antibodies (RF+/ACPA+) (3.27(1.25-8.53)) were significantly correlated with JSN progression. In patients <40 baseline swollen joint count (SJC) (1.09(1.01-1.18)) and ESR over time (1.04(1.02-1.06)) were significantly associated.

Conclusion

At baseline, RA patients ≥55 years had more JSN than younger patients but after 10 years JSN scores were similar between age-groups. Independent risk factors for JSN progression were baseline SJC and ESR over time in patients <40, RF+/ACPA+ and ESR over time in patients ≥55 years. This suggests that mechanisms leading to JSN progression are related to (residual) rheumatoid inflammation and vary between age-groups. These mechanisms remain to be elucidated.

INTRODUCTION

Joint damage in rheumatoid arthritis (RA) causes progressive disability in patients.[1] Synovial inflammation activates an immune process that causes articular cartilage degradation leading to joint space narrowing (JSN) and excessive local bone resorption and inadequate bone formation resulting in bone erosions.[2,3] Presence and progression of bone erosions and JSN can be scored using plain radiographs of hands and feet using the Sharp/van der Heijde score (SHS).[4] It is well known that joint damage progression is a result of continued high disease activity.[5] Thus, scoring progression of radiographic damage may affect how efficacy of treatment is interpreted, and can influence therapeutic decisions.

However, progression of JSN, and probably to a lesser extend of erosions, may also be a manifestation of primary osteoarthritis (OA) becoming more prominent with increasing age. Lawrence et al showed age-related increases in radiographic OA in both women (prevalence OA of 7.6% in those aged ≥15<24 versus 97% in patients >65) and men (prevalence OA of 9.4% in those aged ≥15<24 versus 97% in patients >65).[6] OA progression seems to be relatively slow but more frequent and more severe OA progression in the distal and proximal interphalangeal joints of older patients was reported previously.[7,8] No definite clinical progression risk factors for radiographic OA progression are known. More painful joints and more self-reported pain appear to increase radiographic OA progression.[9]

Older RA patients show to have a higher baseline damage score. Khanna et al [10] showed that this was mainly due to more joint space narrowing, and this associated with features of hand osteoarthritis. However Mangnus et al showed that the difference between different age-groups could not be fully explained by JSN.[11] Others reported that patients with a higher age at onset were more often anti-citrullinated protein antibodies (ACPA) positive and had more erosions at baseline, and also higher disease activity scores and higher erosion scores during the first two years of treatment.[12,13] Still others showed that in advanced RA, older patients had more JSN than younger patients.[14]

We hypothesized that JSN progression may show a different pattern in older than in younger RA patients. In addition predictors of JSN may be different between these age-groups, due to primary osteoarthritis becoming more prominent with increasing age. We aimed to identify and compare age-specific baseline risk factors for the development of JSN in patients who participated in the BeSt study, a multicenter randomized clinical trial. Early RA patients were treated according to one of four dynamic treatment strategies all aiming a low disease activity (Disease Activity Score: DAS≤2.4). Patients were followed for 10 years and radiographs of hands and feet were obtained annually to score the bone erosions and JSN by the SHS.

PATIENTS AND METHODS

Subjects and design

The BeSt (Dutch acronym for treatment strategies) a multicenter, randomized clinical trial included 508 patients with recent-onset active rheumatoid arthritis (1987 revised American College of Rheumatology criteria [15]) and a symptom duration ≤2 years. All participants gave written informed consent and the medical ethics committee of each participating centre approved the study protocol.

Patients were randomized into four treatment strategies: 1. sequential monotherapy, 2. step-up combination therapy, 3. initial combination therapy with methotrexate, sulfasalazine and prednisone and 4. initial combination therapy with methotrexate and infliximab. Treatment adjustments were made every three months aiming at a DAS <2.4. If DAS was ≤2.4 for six months, treatment could be tapered to maintenance dose, and if then DAS <1.6 was achieved for another six months, medication was discontinued. Once the DAS was ≥1.6 treatment was restarted. Details of the BeSt study have been published elsewhere.[16,17]

Methods of measurement

At baseline, rheumatoid factor (RF) status was evaluated. ACPA status was determined afterwards by the anti-cyclic citrullinated peptide test (anti-CCP2) in available stored baseline serum samples. Health assessment questionnaires (HAQ) [18] and the DAS were assessed at baseline and every three months for ten years. Baseline and annual radiographs, up to 10 years, of hands and feet were collected and were scored, by two independent readers, blinded for patient identity and time order, using the SHS.[4]

Statistical analysis

Median age at baseline in our population was 54.9 years. Based on this median, and considering the unlikelihood of osteoarthritis in patients <40 years old [6] three arbitrary subgroups were created: ‘group <40’ comprising patients aged <40 years, ‘group ≥40<55’ with patients ≥40 years but <55 years and ‘group ≥55’ with patients ≥55 years old at baseline. Baseline characteristics were compared with the multinomial variable ‘age-group’ by the χ^2 test, one-way analysis of variance and Mann-Whitney U test. Pairwise comparisons between the age-groups were performed with the χ^2 test, *t*-test and Kruskall-Wallis test. Mean SHS, Erosion and JSN (progression) scores after 10 years were compared between groups using one-way analysis of variance, with robust standard error estimation and p-values because of the skewed non-normal distributions.

After ten years, DAS and HAQ were known for 292/508 patients, and radiographs were available for 278/508 patients. To avoid bias due to missing data, multiple imputation techniques were performed. The imputed values are based on all radiographs in the study,

and are consequently less sensitive to one measurement error or picture of low quality. To improve resemblance to the normal distribution, annual JSN and erosion scores were log-transformed before imputing. The imputation model incorporated the baseline variables: age, sex, body mass index (BMI), smoking status, randomisation arm, RF status, ACPA status, log-transformed erosion and narrowing score, HAQ score and the components of the DAS. Annual log-transformed erosion and narrowing scores, 10-year HAQ scores and bi-annual DAS were also included in the imputation model.

SHS and JSN scores are always whole non-negative numbers and therefore, JSN progression scores are integers. In our study only 2.2% of the progression scores were negative, hence JSN progression is approximately a count. Furthermore, 37% of the patients had zero JSN progression. For regression modelling of the JSN progression, we used robust Poisson regression after setting the negative progressions to zero. This regression method assumes that the covariates have a multiplicative effect on the mean progression scores, but remains valid if the Poisson is violated. We report the exponentiated regression coefficients, which are interpreted as ratios of means (relative to the reference category for categorical predictors, or corresponding to a one unit increase for numerical predictors). When analyses group were done separately for each age-group we applied Bonferroni correction to adjust for multiple testing.

In the multivariate analysis RF status and ACPA status were coded into one variable because both antibodies are frequently present in the same patients and consequently their influence is confounded by the effect of the other antibody. Since treatment strategy is randomly allocated, it does not confound the effect of other variables and was therefore not included in the multivariate models. All risk factors with a p-value <0.2 were entered in the multivariate models with Bonferroni correction to correct for multiple testing. Accordingly, predictor variables with p-values <0.0167 were considered significant, 98.33% confidence intervals are given, and only predictor variables with univariate p-values <0.066 were entered in the multivariate model. Since we selected our regression variables carefully, we did not remove the determinants from the multivariate analysis when they did not attain significance. Analyses were performed with SPSS 20.0.

RESULTS

Baseline

In the BeSt study, 508 patients were included, 81 (16%) aged <40, 179 (35%) aged ≥40<55 and 248 (49%) aged ≥55. Mean age at baseline was 33, 49 and 66 in the three age-groups, respectively. Table 1 shows the baseline characteristics of the three age-groups.

Table 1: Baseline characteristics in the different age-groups.

	Group <40	Group ≥40<55	Group ≥55	p-value
	n=81	n=179	n=248	
Age. mean ± SD years	33 ± 6	49 ± 5	66 ± 8	
Women. no. (%)	61 (75)	125 (70)	157 (63)	0.10
Smoking. no.(%)	25 (30)	78 (44)	74 (30)	0.01
BMI. mean ± SD	24.4 ± 4.3	26.6 ± 4.5	26.1 ± 3.8	0.001
Time from diagnosis to inclusion. median weeks (IQR)	1.6 (0.7-3.1)	2.4 (1.0-5.3)	2.7 (1.0-4.7)	0.004
Symptom duration. median weeks (IQR)	26.1 (13.4-57.9)	24.6 (15.3-56.1)	22.4 (13.3-44.3)	0.25
RF positive. no. (%)	53 (65)	123 (69)	153 (62)	0.32
ACPA positive no./total no. (%)	43/78 (55)	116/169 (69)	132/226 (58)	0.05
DAS. mean ± SD	4.4 ± 0.9	4.3 ± 0.8	4.5 ± 0.9	0.12
HAQ score. 0-3 scale. mean ± SD	1.3 ± 0.7	1.4 ± 0.6	1.4 ± 0.7	0.49
CRP. mean ± SD	35.4 ± 43.2	32.8 ± 41.9	41.1 ± 43.2	0.14
ESR. mean ± SD	37.1 ± 25.4	34.7 ± 25.7	45.8 ± 28.4	<0.001
Ritchie articular index	14 (9-20)	13 (10-17)	13 (9-18)	0.53
Swollen joint count	14 (10-18)	12 (9-18)	14 (10-19)	0.06
Total SHS. 0-448 scale				
median (IQR)	1.0 (0.0-3.0)	1.0 (0.0-4.5)	2.5 (1.0-7.4)	<0.001
mean ± SD	2.4 ± 3.7	3.1 ± 4.9	5.0 ± 6.8	
Erosion score. 0-280 scale				
median (IQR)	0.0 (0.0-0.3)	1.0 (0.0-3.0)	0.0 (0.0-1.0)	<0.001
mean ± SD	0.5 ± 1.4	0.9 ± 2.6	1.1 ± 2.0	
JSN score. 0-168 scale				
median (IQR)	0.3 (0.0-3.0)	1.0 (0.0-3.0)	2.0 (0.0-6.0)	<0.001
mean ± SD	1.9 ± 2.9	2.2 ± 3.2	3.9 ± 5.5	
Treatment strategy				
Sequential monotherapy, no. (%)	19 (24)	51 (29)	56 (23)	0.52
Step-up therapy, no. (%)	18 (22)	47 (26)	56 (23)	
Initial combination therapy with prednisone, no. (%)	22 (27)	45 (25)	66 (27)	
Initial combination therapy with infliximab, no. (%)	22 (27)	36 (20)	70 (28)	

RF: rheumatoid factor, ACPA: Anti–citrullinated protein antibodies, DAS: disease activity score, HAQ: health assessment questionnaire, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SHS: Sharp/van der Heijde score, JSN: joint space narrowing, SD: standard deviation, IQR: interquartile range.

The variables that were statistically significantly associated with the multinomial variable 'age-group' (<40, ≥40<55 and ≥55), showed statistically significant differences when compared pairwise between age-groups. 30%, 44% and 30% of the three age-groups participants were noted as 'smokers' at baseline (group ≥40<55 vs. group ≥55, p=0.004). Mean BMI was 24.4 in group <40, 26.6 in group ≥40<55 (group <40 vs. group ≥40<55, p<0.001) and in 26.1 in group

≥55 (group <40 vs. group ≥55, p=0.001). Erythrocyte sedimentation rate (ESR) was higher in group ≥55 compared to group <40 (mean 46 vs. 37 ; p=0.01) and group ≥40<55 (mean 46 vs. 35; p<0.001). Time from diagnosis was lower in group <40 compared to group ≥40<55 and group ≥55 (p=0.002 and p=0.004 respectively).

Pairwise age-group comparison of the variables not statistically significantly associated with 'age-group' was performed, but showed no statistically significant differences between groups except for DAS and swollen joint count (SJC) (data not shown). Age-group <40 had similar baseline DAS and SJC compared to groups ≥40<55 and ≥55. Group ≥40<55 had lower DAS compared to group ≥55 (4.3 vs. 4.5; p=0.04) and a lower baseline SJC compared to group ≥55 (median (interquartile range IQR) (12 (9-18) vs. 14 (10-19); p=0.02)). More patients were ACPA positive in group ≥40<55 than in group <40 (68% vs. 55%; p=0.05) and group ≥55 (68% vs 58%; p=0.05). Both ACPA and RF were present in 46%, 60% and 48% of the patients in group <40, group ≥40<55 and group ≥55, respectively.

All baseline radiographic scores were similar in group <40 and group ≥40<55. Baseline SHS score was higher in group ≥55 (median 2.5, IQR 1.0-7.4) compared to the other groups (group <40: 1.0 (0.0-3.0); group ≥40<55: 1.0 (0.0-4.5; p<0.001). Baseline erosion scores were higher in group ≥55 compared to group ≥40<55 (1.0 (0.0-3.0) vs. 0.0 (0.0-1.0); p=0.006) and group <40 (0.0 (0.0-0.3); p<0.001). Also, more patients in group ≥55 had JSN ≥0.5 (70% vs 50% in group <40; p=0.001; and 55% in group ≥40<55; p=0.002) and the median JSN score was higher compared to the other groups (2.0 (0.0-6.0) in group ≥55 vs. 0.3 (0.0-3.0) in group <40 and 1.0 (0.0-3.0) in group ≥40<55; p<0.001). JSN in the proximal interphalangeal joints increased with age: (mean ± SD) 0.1 ± 0.5 (median (IQR) 0.0 (0.0-0.0)) in group <40, 0.2 ± 0.5 (0.0 (0.0-0.0)) in group ≥40<55 and 0.4 ± 0.9 (0.0 (0.0-0.5)) group ≥55 (<40 vs. ≥40<55 p=0.06; <40 vs. ≥55 p=0.001; ≥40<55 vs. ≥55 p= 0.02). This trend was not observed in the metacarpophalangeal joints. JSN scores in metacarpophalangeal joints are higher in group ≥55 compared to group ≥40<55 (0.6 ± 1.2 (0.0 (0.0-1.0)) vs. 0.4 ± 0.9 (0.0 (0.0-0.0)), p=0.01) but not compared to group <40 (0.5 ± 0.9 (0.0 (0.0-1.0)); <40 vs. ≥55 p=0.51)

Outcomes after ten years

Ten-year follow-up characteristics are shown in table 2. Average DAS over time was similar in all groups. ESR over time was higher in group ≥55 (mean 22) compared to the other groups (mean 17 <40 and mean 18 in group ≥40<55; p=0.01 group <40 vs. ≥55, p<0.01 group ≥40<55 vs. ≥55). After ten years of follow-up none of the mean radiographic scores differed between the age-groups but JSN ≥ 0.5 was found more often in group ≥55 (90%) compared to group <40 (75%) and in group ≥40<55 (80%) (p=0.001 and p=0.008, respectively).

Table 2: Outcomes 10 years after randomisation

	Group <40	Group ≥40<55	Group ≥55	p-value <40 vs ≥40<55	p-value <40 vs ≥55	p-value ≥40<55 vs ≥55
	n=81	n=179	n=248			
DAS over time. mean ± SD	2.0 ± 0.7	2.0 ± 0.6	2.1 ± 0.6	0.68	0.57	0.18
ESR over time. mean ± SD	17.2 ± 12.3	17.8 ± 11.6	22.1 ± 16.1	0.73	0.01	<0.01
Total SHS. 0-448 scale						
median (IQR)	4.1 (1.2-12.5)	6.5 (2.0-15.5)	7.0 (3.0-15.5)	0.69	0.57	0.75
mean ± SD	15.0 ± 32.4	13.5 ± 20.3	12.9 ± 17.1			
SHS progression						
median (IQR)	2.7 (0.0-7.0)	3.0 (0.5-11.7)	2.5 (0.5-8.4)	0.54	0.19	0.15
mean ± SD	12.6 ± 31.0	10.4 ± 18.5	7.8 ± 15.9			
Erosion score. 0-280 scale						
median (IQR)	1.0 (0.0-3.8)	1.3 (0.3-5.0)	1.5 (0.5-4.0)	0.91	0.37	0.07
mean ± SD	4.9 ± 13.0	5.1 ± 9.6	3.6 ± 6.5			
Erosion progression						
median (IQR)	0.8 (0.0-3.0)	1.0 (0.0-4.0)	0.8 (0.0-2.1)	0.93	0.20	0.02
mean ± SD	4.3 ± 12.7	4.2 ± 8.1	2.5 ± 6.2			
JSN score. 0-168 scale						
median (IQR)	3.0 (0.5-8.0)	4.0 (1.0-10.0)	5.3 (2.0-11.5)	0.48	0.73	0.47
mean ± SD	10.1 ± 20.4	8.4 ± 12.4	9.4 ± 12.0			
JSN progression						
median (IQR)	1.0 (0.0-5.0)	1.9 (0.0-7.5)	1.8 (0.0-5.5)	0.36	0.20	0.49
mean ± SD	8.2 ± 19.3	6.2 ± 11.6	5.4 ± 11.2			

DAS: disease activity score. ESR: erythrocyte sedimentation rate. SHS: Sharp/van der Heijde score. JSN: joint space narrowing. SD: standard deviation. IQR: interquartile range.

SHS progression was similar in all groups (2.7 (0.0-7.0); 3.0 (0.5-11.7); 2.5 (0.5-8.4)). Erosion progression scores were higher in group ≥40<55 compared to group ≥55 (1.0 (0.0-4.0) vs. 0.8 (0.0-2.1); p=0.02). JSN progression did not differ statistically significantly between the age-groups: (mean ± SD) 8.2±19.3 (median (IQR) 1.0 (0.0-5.0)) in group <40, 6.2±11.6 (1.9 (0.0-7.5)) in group ≥40<55 and 5.4±11.2 (1.8 (0.0-5.5)) in group ≥55. Scores at ten-year and progression scores are shown in figure 1. While the median progression scores are higher in the oldest groups, JSN progression scores are more skewed to the right (higher progression scores) in the youngest group, as reflected by a higher mean and higher standard deviation in that group.

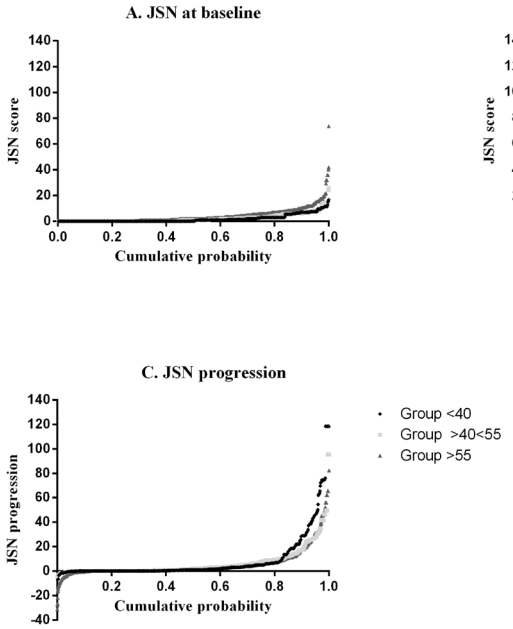

Figure 1 Probability plots JSN score at baseline (A), ten years (B) and progression (C) for the different age-groups (Darkest dots: group <40, lightest dots group ≥40<55, intermediate dots: group ≥55)
JSN: joint space narrowing.

Predictive factors for JSN progression

Univariate risk factors that were statistically significantly associated with JSN progression in group <40 were JSN at baseline (RR (IQR)) (1.17 (1.01-1.35)), baseline SJC (1.11 (1.02-1.21)), ACPA+ (3.79 (1.21-11.89)), RF+/ACPA+ (5.39 (1.25-23.15)) and average ESR over time (1.04 (1.00-1.08)) (table 3) and initial combination therapy with infliximab was protective against JSN progression compared to sequential monotherapy (0.20 (0.04-0.95)). In group

≥40<55, erosions at baseline (1.06 (1.01-1.12)), RF+ (2.88 (1.40-5.96)), RF+/ACPA+ (3.41 (1.33-8.71)) and average ESR (1.02 (1.00-1.04)) were correlated with JSN progression. Also, initial combination therapy with infliximab (0.49 (0.19-1.27)) compared to sequential monotherapy tended to protect against JSN progression in group ≥40<55. In group ≥55, smoking (2.00 (1.11-3.58)), RF+ (2.63 (1.31-5.28)), ACPA+ (3.39 (1.58-7.28)), RF+/ACPA+ (4.19 (1.58-11.07)) and average ESR (1.02 (1.01-1.03) were statistically significantly related to JSN progression. Treatment strategies were not correlated with JSN progression in group ≥55.

Table 3: Univariate Poisson regression analysis per age-group

	Group <40		**Group ≥40<55**		**Group ≥55**	
	RR	**95% C.I.**	**RR**	**95% C.I.**	**RR**	**95% C.I.**
Baseline						
smoking	0.83	(0.16-4.23)	1.18	(0.60-2.32)	2.00	(1.11-3.58)
BMI<25	Ref		Ref		Ref	
BMI>25<30	0.91	(0.22-3.82)	0.58	(0.37-1.50)	1.12	(0.58-2.14)
BMI>30	0.28	(0.05-1.66)	0.74	(0.19-1.73)	1.19	(0.50-2.87)
Ritchie articular index	1.00	(0.94-1.06)	0.95	(0.89-1.01)	0.98	(0.93-1.03)
Swollen joint count	**1.11**	**(1.02-1.21)**	0.97	(0.93-1.01)	1.01	(0.98-1.05)
JSN	**1.17**	**(1.01-1.35)**	1.06	(0.99-1.14)	1.00	(0.94-1.07)
Erosions	1.13	(0.90-1.41)	**1.06**	**(1.01-1.12)**	1.02	(0.89-1.15)
RF-/ACPA-	Ref		Ref		Ref	
RF+/ACPA-	1.65	(0.28-9.82)	3.31	(0.93-11.75)	1.47	(0.48-4.47)
RF-/ACPA+	2.78	(0.48-16.15)	1.76	(0.54-5.79)	2.52	(0.84-7.54)
RF+/ACPA+	**5.39**	**(1.25-23.15)**	**3.41**	**(1.33-8.71)**	4.19	(1.58-11.07)
RF-	Ref		Ref		Ref	
RF+	2.81	(0.90-8.77)	**2.88**	**(1.40-5.96)**	2.63	(1.31-5.28)
ACPA-	Ref		Ref		Ref	
ACPA+	**3.79**	**(1.21-11.89)**	2.02	(0.94-4.33)	3.39	(1.58-7.28)
Average ESR over time	1.04	(1.00-1.08)	**1.02**	**(1.00-1.04)**	1.02	(1.01-1.03)
Sequential monotherapy	Ref		Ref		Ref	
Step up to combination therapy	0.44	(0.07-2.79)	1.29	(0.56-3.02)	0.81	(0.34-1.93)
Initial combination therapy with prednisone	0.89	(0.20-3.93)	0.77	(0.36-1.64)	0.93	(0.38-2.25)
Initial combination therapy with infliximab	**0.20**	**(0.04-0.95)**	0.49	(0.19-1.27)	0.84	(0.36-2.00)

BMI: body mass index, JSN: joint space narrowing, RF: rheumatoid factor, ACPA: Anti–citrullinated protein antibodies, ESR: erythrocyte sedimentation rate; Erosions: erosion score (SHS); RR.: relative risk, 95% C.I.: 98.33% (Bonferroni correction) confidence interval.

Risk factors with a p-value <0.067 were entered in the multivariate analysis per age-group (table 4). In the multivariate Poisson regression, in group <40 baseline SJC (1.09 (1.01-1.18)) and average ESR (1.04 (1.02-1.06)) were independently associated with JSN progression. In group ≥40<55 none of the risk factors were significantly correlated, but the influence of the combined presence of RF and ACPA showed a trend (4.00 (0.88-18.10)). In group ≥55 ten-

year average ESR (1.02 (1.00-1.03)) and the combined presence of RF and ACPA (3.27 (1.25-8.53)) were significantly associated with JSN progression. If only baseline variables were incorporated in the multivariate model, similar results were yielded, however the influence of the combined presence of RF and ACPA in group ≥40<55 attained significance. (data not shown).

Table 4: Multivariate Poisson regression analysis per age-group

Group <40	**RR**	**95% C.I.**
Baseline JSN	1.07	(0.95-1.22)
Swollen joint count	**1.09**	**(1.01-1.18)**
RF- /ACPA-	Ref	
RF+ /ACPA-	1.80	(0.29-11.25)
RF- /ACPA+	3.14	(0.34-28.66)
RF+/ACPA+	4.00	(0.88-18.08)
Time average ESR	**1.04**	**(1.02-1.06)**
Group ≥40<55	**RR**	**95% C.I.**
Baseline JSN	1.02	(0.95-1.10)
Baseline Erosions	1.04	(0.98-1.10)
Ritchie articular index	0.96	(0.89-1.03)
Swollen joint count	1.00	(0.95-1.10)
RF- /ACPA-	Ref	
RF+ /ACPA-	2.67	(0.76-9.39)
RF- /ACPA+	1.28	(0.37-4.43)
RF+/ACPA+	2.65	(0.95-7.38)
Time average ESR	1.01	(0.99-1.04)
Group ≥55	**RR**	**95% C.I.**
Smoking at baseline	1.46	(0.81-2.63)
RF- /ACPA-	Ref	
RF+ /ACPA-	1.33	(0.45-3.98)
RF- /ACPA+	2.31	(0.75-7.10)
RF+/ACPA+	**3.27**	**(1.25-8.53)**
Time average ESR	**1.02**	**(1.00-1.03)**

RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; JSN: joint space narrowing; RR: relative risk; 95% C.I.: 95% confidence interval after Bonferroni correction.

DISCUSSION

Radiographic damage progression, as potential cause of permanent disability, is an important target for preventive therapy and one of the main determinants of successful treatment in patients with rheumatoid arthritis. However, in some RA patients primary osteoarthritis (OA), represented by joint space narrowing may contribute to radiographic joint damage progression. Previous cross sectional studies [10-12,14] have shown that older RA patients had higher damage

scores than younger RA patients at baseline, partly explained by higher JSN [10,11] In addition radiographic OA is more often present in older patients and progression is more frequent and more severe in older patients. Risk factors for OA progression differ from risk factors for RA progression.[6-8]
We hypothesized that older RA patients also show more JSN progression over time than younger patients, because progression in JSN is caused by both RA and OA, and that progression of JSN was associated with different risk factors in different age-groups.
To investigate our hypothesis, we compared the severity of JSN between the age-groups and tried to identify age-group-specific risk factors in a cohort of patients with recent onset RA (1987 criteria), who were treated to target DAS≤2.4 over the course of 10 years, with three-monthly DAS calculation and treatment adjustments, and radiographs of hands and feet taken at baseline and yearly thereafter. JSN scores were derived from the Sharp/van der Heijde score.

As expected, we found that RA patients of ≥55 years old showed JSN more often and more severe JSN at baseline than younger patients. It was shown that while damage to the proximal interphalangeal joints at baseline increases with age, damage to the metacarpophalangeal joints does not. Older patients had higher ESR, higher SJC, higher DAS and a higher baseline erosion score suggesting that in older patients there was more rheumatoid inflammation. After 10 years, there were no statistically significant differences between the age-groups in the amount of JSN progression, but JSN progression was more skewed to the right in the youngest group, as reflected by a higher mean and higher standard deviation in that group. Risk factors for JSN progression were only slightly different in the three age-groups. In patients ≥55 years, presence of RF and ACPA and a high ESR as marker for systemic inflammation over time were independent risk factors for JSN progression. Also in patients <40 years, high inflammatory activity, represented by baseline SJC and ESR over time, was independently associated with JSN progression, but presence of auto-antibodies was not. In the >40 ≤55 years age-group there were no independent predictors for JSN progression.
These results confirm previous reports that JSN is more prevalent and more severe in older RA patients than in younger patients at baseline. However, contrary to our hypothesis, we did not find more JSN progression in older patients. In fact, the most severe JSN progression was observed in (a subgroup of) patients <40 years. Slow progression observed in (a subgroup of) older patients may in part represent JSN due to primary osteoarthritis, which has been shown to be slowly progressive and more prevalent in older patients.[7,8,19]
This hypothesis is supported by the fact that, although ESR over time was higher in the oldest group than in the other age-groups, as is observed in healthy individuals,[20] DAS over time was not, indicating that the swollen joint counts and Ritchie Articular Index results over time were low.

RA appears to have been well suppressed in the older patients, which is also suggested by the finding that the mean erosion progression score was lower than in the other age-groups. Primary osteoarthritis is supposed to be relatively rare in the ≤40 years age-group, but over 10 years follow up may have progressively occurred, adding to the increased JSN progression scores due to inflammation in those patients. However, in the younger patients erosion progression scores were also higher, suggesting that from baseline, when they had a higher SJC, over 10 years follow up, when they had similar DAS but lower ESR, RA may have been insufficiently suppressed. That initial combination therapy in the older patients is not associated with less JSN progression may suggest that JSN progression in older patients is caused by osteoarthritis which is less susceptible to the treatment with TNF-inhibitors.[21] However, in older patients, combined presence of RF and ACPA was associated with more damage progression. In general, these antibodies have been associated with a more destructive disease course in RA. A previous analysis of the BeSt study [22] showed that presence of ACPA did not affect the suppression of inflammation, but even in patients with similar low disease activity was associated with more damage progression. Why this is not found for younger patients in this study remains to be investigated, but might be explained by the smaller sample size in the age-group <40.

Previous studies have looked at the possible contribution of primary osteoarthritis to JSN scores in RA patients [14,23,24] by multivariate linear analysis adjusted for age. This statistical method assumes a linearity of the relationship between age and outcome that may not exist in the oldest patients [25] and does not take into account the non-linear interaction between some risk factors and age. By stratifying into different age-groups, we could assess non-linear relations between age and risk-factors. The downside of our method is a loss of power and the loss of differentiation between ages that belong in one age-group. The age limits per group were set arbitrarily, in part based on the median age in the total group (55 years), the need for sufficient numbers of patients per group and the presumption that significant primary osteoarthritis is unlikely in patients under 40 years old. We were able to follow patients for 10 years, whereas previous studies had shorter follow up periods. During these 10 years all patients received treatment targeted at a Disease Activity Score ≤2.4. This resulted, as previous analyses [26] have shown, in similarly well controlled rheumatoid disease activity in all patients in the four strategy arms from 1 year on.

It can be argued that to distinguish primary osteoarthritis from rheumatoid joint damage, one of the specific scoring methods for osteoarthritis should have been used.[19] These however may also include rheumatoid joint damage in the score, and it remains unclear which is the best method to score osteoarthritis progression. Instead, we looked at joint space narrowing as part of the Sharp/van der Heijde score (SHS), precisely to highlight that a method to measure outcomes of RA treatment can be susceptible to overestimation of rheumatoid damage by including osteoarthritis. Our hypothesis that JSN in older patients is caused by both RA and

OA was supported by increasing JSN at baseline in the proximal interphalangeal joints but not in the metacarpophalangeal joints. However, the potentially combined presence of rheumatoid damage and osteoarthritic features suggest that risk factors identified in our analyses might also be risk factors for both causes of JSN progression.

In conclusion, in different age-groups of patients with rheumatoid arthritis, joint space narrowing scores and progression of joint space narrowing may be influenced by various factors, one of which may be primary osteoarthritis in the older age-groups. This may affect how radiographic scoring methods can be interpreted to represent treatment effects of anti-rheumatic therapy in different age-groups. In all patients, inflammation should be optimally suppressed to avoid progression of joint damage which may determine long term functional ability. At baseline disease seems to be more severe in older persons, but after 10 years, radiographic outcomes do not differ between age-groups, implicating that progression in the younger patients might not be optimally suppressed. Finally, a possible association between inflammation and progression of osteoarthritis should be further investigated by including specific osteoarthritis scoring methods and by evaluation in other cohorts, as this knowledge may open a door to preventive treatment.

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